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Model for Simulating Fasting Glucose in Type 2 Diabetes and the Effect of Adherence to Treatment [1]

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Abstract: The primary goal of this paper is to predict fasting glucose levels in type 2 diabetes (T2D) in long-acting insulin treatment. The paper presents a model for simulating insulin-glucose dynamics in T2D patients. The model combines a physiological model of type 1 diabetes (T1D) and an endogenous insulin production model in T2D. We include a review of sources of variance in fasting glucose values in long-acting insulin treatment, with respect to dose guidance algorithms. We use the model to simulate fasting glucose levels in T2D long-acting insulin treatment and compare the results with clinical trial results where a dose guidance algorithm was used. We investigate sources of variance and through simulations evaluate the contribution of adherence to variance and dose guidance quality. The results suggest that the model for simulation of T2D patients is sufficient for simulating fasting glucose levels during titration in a clinical trial. Adherence to insulin injections plays an important role considering variance in fasting glucose. For adherence levels 100%, 70% and 50%, the coefficient of variation of simulated fasting glucose levels were similar to observed variances in insulin treatment. The dose guidance algorithm suggested too large doses in 0.0%, 5.3% and 24.4% of cases, respectively. Adherence to treatment is an important source of variance in long-acting insulin titration.

Keywords: Biomedical systems, Diabetes, Physiological models, Medical applications, Type 2 Diabetes.

1. INTRODUCTION

Patients with type 2 diabetes (T2D) initiating insulin treatment typically inject long-acting insulin once daily to lower fasting glucose (FG) concentration. To determine the individual patients optimal daily dose, patients increase doses based on self-monitored blood glucose (SMBG), until the desired FG level is reached. This process is called titration, and is a delicate procedure. The effect of too little doses of insulin is hyperglycemia. Untreated hyperglycemia can cause long term complications which include cardiovascular disease, neuropathy, kidney damage and other complications. Too high doses of insulin can lead to hypoglycemia. In mild cases, hypoglycemia will cause confusion and seizures. In severe cases it may cause coma or death. The main challenges in insulin titration include complexity of regimen and dose calculations, fear of hypoglycemia, the need for frequent SMBG measurements and lack of confidence (Arnolds et al., 2013). This leads to too seldom dose adjustments and titration can take years if successful at all (Bashan et al., 2011).

To address the need for titration assistance, a number of research and industrial groups have developed automatic algorithms for dose guidance (Bergenstal et al., 2012; Cook et al., 2005; Bajaj et al., 2016). SMBG measurements have been demonstrated to be sufficient to adjust insulin dosage, provided that insulin adjustments are modest (Bergenstal et al., 2012). However, variance in SMBG not only stems from device accuracy but also biological and drug-related day-to-day variance, measuring technique and lifestyle changes. If the measured FG levels are high, the algorithms recommend an increase in insulin dose by a certain amount. Similarly, if the FG is low, the dose is decreased. The algorithms assume that the input, i.e. FG levels, is correlated with the response to the output, i.e. recommended dose. We therefore hypothesize that current titration algorithms are suboptimal with respect to high variance in glucose levels.

The motivation of this paper is to present an overview of the sources of variance in FG levels during insulin initiation and intensification, and to create a simulation model for use in development of safe and effective titration algorithms, and to evaluate the contribution of adherence in FG variance.

In this paper, Section 2 presents a review and suggested categorization of variances in long-acting insulin titration for T2D patients. In Section 3 we suggest a model of glucose-insulin dynamics to generate a cohort of T2D patients initiating long-acting insulin treatment. In Section 4 we present the results of comparing simulation results with a clinical trial. We also evaluate the effect of adherence on safety in dose guidance. Section 5 presents a short conclusion of the methods and results.

2. SOURCES OF VARIANCE

A key challenge in adaptive glucose control is to determine dose sizes based on data with large day-to-day variability. Variability is caused by different factors, and some are easier to mitigate than others. Lifestyle and physiological state are closely related, and the sources of variance are therefore difficult to completely separate. Kildegaard et al. (2009) divided sources of variance in T1D into five categories; metabolic, insulin, glucose monitoring and meal variability, and lifestyle and compliance. Here we divide sources into three categories, each discussed in the following subsections; 1) metabolic variability including insulin variability, 2) variations due to lifestyle and adherence and 3) device related variability.

2.1 Metabolic variability

Glucose metabolism depends on the physiological state of the body. Stress causes the release of a number of hormones that elevate glucose levels, while exercise and weight loss increase insulin sensitivity (Guthrie and Guthrie, 2009).

Non-insulin related variability
Research groups have previously investigated day-to-day and intraday glucose variability in patients with T2D. In a study by Ollerton et al. (1999), day-to-day FG variability in newly diagnosed T2D patients not receiving diabetes medication was approximately 14%. They also found that high levels of FG are correlated with higher glucose variance.

Studies on healthy humans have suggested that daily fluctuations in insulin sensitivity contribute to variations in glucose uptake. For instance, Gibson and Jarrett (1972) found that fall in blood sugar following doses of 0.05-0.1 IU/kg was significantly less for normal weight humans in the afternoon than in the morning. The observed difference was around 0.5-1.0 mmol/L. For obese individuals, their results suggested that this difference decreased with higher weight.

Insulin related variability
Basal insulin preparations act in different ways, and have different pharmacokinetic (PK) and pharmacodynamic (PD) characteristics. Some long acting insulin types crystallize subcutaneously (SC) after injection, and slowly dissolve to enter the blood stream. These insulins are prone to high day-to-day PK/PD variability due to great variability in the break-down process. Newer insulins allow less variability by forming soluble chains in the skin, which then slowly release insulin into the circulation, (Heise et al., 2012). Fig. 1 illustrates day-to-day coefficient of variation
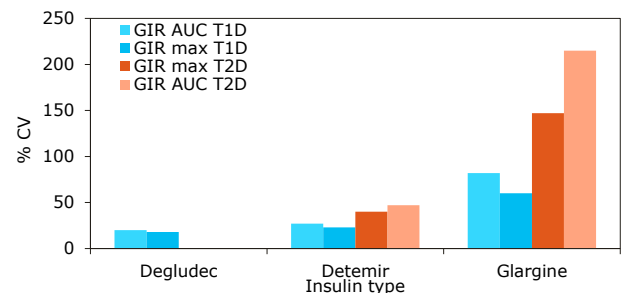

Fig. 1. Day-to-day CV in pharmacodynamics of degludec, detemir and glargine. GIR AUC and GIR max are glucose infusion rate area under the curve and maximum value (Heise et al., 2012; Klein et al., 2007).

(CV) in PD for T1D and T2D, for a number of long acting insulins on the market. For glargine, the CV is around 150% for maximum glucose infusion rate (GIR), while for detemir it is reduced to around 40%. The variations in T2D are greater than in T1D for detemir and glargine, but no data is available for degludec in T2D.

One source of variation during insulin treatment initiation is the dawn phenomenon. Extensive studies have shown that it is a frequent event across the population of T2D patients on oral treatment (Monnier et al., 2013). In a clinical trial with T2D patients on metformin only, glucose levels were monitored overnight while initiating and intensifying insulin treatment. The results showed that in non-insulin treated patients, FG levels increased overnight by approximately 20 mg/dl over 4-5 hours. However, after 6 months of insulin treatment intensification the phenomenon was eliminated (Monnier et al., 2013). Therefore its effect are only apparent early in the treatment. Degludec is ultra-long acting insulin with a half-life of over 25 hours. The long half-life causes the drug to reach steady state after 2-3 days, (Heise et al., 2015). This means that there is day-to-day variance in the FG measurements following a dose size change, and the full response to a new dose size is reached in 2-3 days. The overlap decreases random variation which, theoretically, results in a more stable treatment. Additionally, forgetting a dose is less critical than with previous drugs due to the long overlap from the previous injections (Haahr and Heise, 2014).

2.2 Lifestyle and adherence

Basal insulin treatment is complex and requires extensive work from the patient. For many patients, this is a disruption of life prior to diagnosis, where they are required to manage dose calculations and daily do SMBG and injections. A study that investigated variance in glucose levels of T2D subjects on stable basal insulin doses, observed a total CV in FG of 35%. The results indicated that factors including consumption of sugars and adherence to treatment were highly correlated with FG variance, explaining 21% of the CV, (Murata et al., 2004). Furthermore, insulin sensitivity is correlated with level of activity, stress and illness, and thereby glucose levels.

Adherence
Adherence to treatment is essential to successful glycemic control and collecting reliable data on the level of adherence is difficult (Cramer and Pugh, 2005).
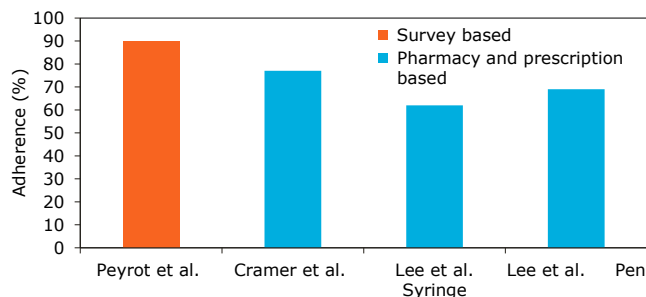
Fig. 2. Adherence measured as percentage of doses taken compared to regimen (Cramer and Pugh, 2005; Lee et al., 2006; Peyrot et al., 2012).

In a study by Peyrot et al. (2012) based on an Internet survey of physicians and diabetes patients, around 30% of patients reported insulin omission 3.3 days in the last month, and around 75% of physicians reported that their patients on average omitted basal insulin 4.3 days per month. A total rate of omission was estimated to be 3.1 days, which corresponds to approximately 90% adherence to once-daily insulin treatment. Another study used pharmacy databases and prescription data and found that insulin use was 77% of the prescribed amount. They furthermore found that significant predictors for adherence included HbA1c levels, race and treatment intensity (Cramer and Pugh, 2005). Another study on adherence based on pharmacy and clinic databases found that adherence was 62-69% based on injection device (Lee et al., 2006). Fig. 2 illustrates a summary of results from three studies using different methods to measure adherence.

Lifestyle
Physical activity increases insulin sensitivity. In a study where insulin sensitivity and level of physical activity in untreated T2D patients was investigated, insulin sensitivity was 8% and 25% higher for those who did some moderate and vigorous exercise than sedentary patients, respectively, (Balkau et al., 2008). This is in line with a review of studies on people with T2D, where changes in insulin sensitivity were found to be 23% - 35% after 2 weeks of aerobic training. However, the determining factor of insulin sensitivity is the total daily activity rather than time spent sedentary or doing intensive exercise (Mann et al., 2014).

In a study of FG in T2D patients on stable basal insulin doses, the relationship between variance and meal habits was investigated. No difference in CV was observed between subjects with and without regular mealtimes, or those who sometimes missed meals. CV was however greater in those who consumed more sugars (Murata et al., 2004).

2.3 Device related variability

Standards for accuracy of injection and measurement devices exist (ISO 11608-1:2014, ISO 15197:2013). These standards have tight ranges of accuracy, and need to be reported fulfilled before the devices go to market. However, when in the hands of health care professionals or patients in daily settings, the quality of measurements is different from what is reported in the lab.

Glucose monitoring
Kjome et al. (2010) compared the ISO 15197:2003 with the difference in pharmacy and patient blood glucose measurements. The limits recommended in the standard from 2003 were ±20% for glucose levels equal or over 4.2 mmol/L and ±0.83 mmol/L for lower values. They found that 5% of patients' measurements deviated by more than the recommended 20% from the pharmacy's measurements. They furthermore observed failure to comply with performance guidelines for 50% of the patients. The user errors included failure to clean hands, sampling technique, validity of sampling strips and amount of blood used.

Kildegaard et al. (2009) listed a number of similar studies, for SMBG monitors and continuous glucose monitoring (CGM) devices. They found that the percentage of measurements falling outside the ISO standard for the different monitoring devices varied from under 5% up to around 30%, and CGM measurements showed higher errors. It should be mentioned that even though CGM measurements had larger errors, they provide useful insights into glycemic trends and variations (Kildegaard et al., 2009).

Insulin pens
Accuracy of insulin pens as a source of variance is discussed in e.g. Kildegaard et al. (2009). Insulin pens have shown to have a CV of approximately 2%, when giving a dose of 5U. At large doses, the CV is close to or less than 1%. Heise et al. (2014) studied the impact of volume and speed of subcutaneous injections on perceived pain. They found that backflow after injection was less than 1% CV. Combined with the dosing accuracy of insulin pens, this amount of variance is not likely to be clinically relevant.

3. SIMULATING A COHORT OF T2D PATIENTS

We use the Medtronic Virtual Patient (MVP) model developed by Kanderian et al. (2009) and a meal subsystem described by Hovorka et al. (2004) to simulate a population of virtual T1D patients, and augment this model with an endogenous insulin production compartment to simulate T2D (Ruan et al., 2015). We introduce a method for simulating injections of long-acting insulin in a simulation model intended for pump simulations. The ambition of this model is to represent FG levels in T2D long-acting insulin treatment.

3.1 Type 1 diabetes model

We use two meal compartments, D_1 [mmol] and D_2 [mmol], equivalent to what is described by Hovorka et al. (2004), to describe orally ingested carbohydrates,

$$\frac{dD_1(t)}{dt} = D(t) - \frac{D_1(t)}{\tau_m}, \tag{1a}$$

$$\frac{dD_2(t)}{dt} = \frac{D_1(t)}{\tau_m} - \frac{D_2(t)}{\tau_m}. \tag{1b}$$

τ_m [min] is the peak time of absorption. $D(t)$ [mmol/min] is the amount of ingested carbohydrates per minute. Given the amount of orally ingested carbohydrates $d(t)$ [mg/min], $D(t) = A_G \frac{d(t)}{MwG}$ where $MwG = 180.1559$ [g/mol] is molar weight of glucose and A_G is the unit less CHO bioavailability. We assume 100% bioavailability, $A_G = 1$.

The MVP model is derived from the Bergman minimal model (Bergman et al., 1981). The model consists of four compartments, as described in Kanderian et al. (2009). The insulin absorption subsystem is described by two compartments, I_{SC} [mU/mL] and I_P [mU/mL],

$$\frac{dI_{sc}(t)}{dt} = \frac{1}{\tau_1}\frac{U(t)}{C_I} - \frac{1}{\tau_1}I_{sc}(t), \tag{2a}$$

$$\frac{dI_p(t)}{dt} = \frac{1}{\tau_2}I_{sc}(t) - \frac{1}{\tau_2}I_p(t), \tag{2b}$$

where $U(t)$ [mU/min] is the amount of infused fast acting insulin per minute, C_I [mL/min] is the insulin clearance rate and τ_1 and τ_2 [min] are time constants of insulin flow from injection site to plasma and from plasma and out.

Insulin effect on glucose, I_{EFF} [1/min], and blood glucose concentration, G [mmol/L], are described by

$$\frac{dI_{eff}(t)}{dt} = p_2 S_I I_p(t) - p_2 I_{eff}(t), \tag{3a}$$

$$\frac{dG(t)}{dt} = -(GEZI + I_{eff}(t))G(t) + EGP + R_A, \tag{3b}$$

where p_2 [1/min] is the delay in insulin action after increase in plasma insulin. S_I [mL/mU/min] represents insulin sensitivity. $GEZI$ [1/min] counts for the effect of glucose to lower endogenous glucose production at zero insulin. EGP [mmol/L/min] is the endogenous glucose production rate. V_G [L] is the glucose distribution volume. Rate of appearance of ingested glucose in plasma is $R_A = \frac{D_2(t)}{V_G \tau_m}$ [mmol/L/min].

3.2 Type 2 diabetes augmentation

Ruan et al. (2015) developed six models to describe endogenous plasma insulin concentration based on plasma glucose concentration. We use the base model which assumes constant parameters throughout the day,

$$I_{ENDO}(t) = \frac{M_I(G(t) - G_b) + M_0 G_b}{MCR_I W} \tag{4}$$

I_{ENDO} [mU/L] is the endogenous plasma insulin concentration. $I_S(t)$ [mU/min] is the posthepatic insulin secretion rate. MCR_I [L/kg/min] is the insulin metabolic clearance rate. W [kg] is the subject's body weight. G [mmol/L] is the plasma glucose concentration and G_b [mmol/L] is the fasting plasma glucose concentration. M_I [mU/min/(mmol/L)] is the posthepatic glucose sensitivity and M_0 [mU/min/(mmol/L)] is the basal glucose sensitivity.

This base model assumes a linear relationship between the rate of posthepatic insulin secretion and plasma concentration. The endogenous insulin is added to the insulin in plasma, to affect glucose concentration, so (3a) becomes

$$\frac{dI_{eff}(t)}{dt} = p_2 S_I(I_p(t) + I_{ENDO}(t)) - p_2 I_{eff}(t). \tag{5}$$

To simulate a cohort of 270 patients, we adjust insulin sensitivity and body weight of the first nine patients identified in the MVP model (Kanderian et al., 2009) and choose from the identified parameters of the T2D augmentation (Ruan et al., 2015). The parameter adjustments and choices are listed in Table 1. We use the maximum of average GIR profiles of insulin degludec in T1D and T2D to adjust insulin sensitivity, S_I in the MVP model to

Table 1. Choice of parameter adjustments of the MVP model as defined in Kanderian et al. (2009) and chosen parameter values of the T2D augmentation from Ruan et al. (2015).

	Parameter	Value/Adjustment
$S_{I,T2D}$	[mL/mU]	$[0.3, 0.4, 0.5, 0.6, 0.7] \times S_I$
W_{T2D}	[kg]	$[1.1, 1.2, 1.3, 1.4, 1.5, 1.6] \times W$
MCR_I	[L/kg/min]	0.013
G_b	[mmol/L]	7.0
M_I	[mU/min/(mmol/L)]	0.0
M_0	[mU/min/(mmol/L)]	0.7

represent T2D patients. From results by Haahr and Heise (2014), three hours after injection the maximum GIR of T2D patients is approximately 50% of the maximum GIR of the T1D patients. We choose to adjust insulin sensitivity by 30% to 70%, see Table 1. Similarly we adjust weight based on average BMI values of the patients randomized in the two studies discussed in (Haahr and Heise, 2014), and by assuming equal height of participants. Table 1 presents the body weight adjustments. Distribution volume of glucose is determined by a linear least squares fit, $V_G = aW + b$, using the parameters in Kanderian et al. (2009).

Ruan et al. (2015) present the parameters of complex endogenous augmentation models where parameters are assumed to change during the day. Since here the purpose of the simulation model is to use it in simulating basal insulin titration, which is based on FG measurement, we use the parameters corresponding to the night. The parameters are presented in the bottom three lines of Table 1.

3.3 Long-acting insulin injection

The parameters of the MVP model are fitted to simulate fast acting insulin for simulation of pump infusion. In order to simulate a long-acting insulin injection, we used the PK profile of degludec described by Heise et al. (2012) to define an infusion profile. Degludec has stable PK exposure and glucose-lowering effect over 24 hours, and is detectable in the serum for at least 120 h post-dosing. We simulate the insulin action profile of an injection, U, as follows,

$$u(t) = u_0 \qquad\qquad \text{if } t \le t_0, \tag{6a}$$

$$u(t) = u_0 e^{(t_0-t)/\tau} \qquad\qquad \text{if } t > t_0, \tag{6b}$$

where t_0 is 12 hours, τ is 35 hours and $u_0 = U/(t_0 - t)W$.

4. RESULTS

4.1 Comparison with clinical trial data

We simulate a titration period of 26 weeks, where basal insulin dose is adjusted corresponding to the algorithm presented in Table 2. This setup is similar to a clinical trial of insulin degludec in T2D (Zinman et al., 2012). We add variance to the simulated FG by setting

$$\hat{FG}_t = FG_t + v_t, \tag{7}$$

where $\hat{FG}_t$ and FG_t are simulation with and without biological noise v_t, respectively. In the simulations we assume a best case scenario where no insulin is omitted and biological variance is at minimum. We set $v_t \sim N(0, (0.14 FG_t)^2)$

Table 2. The titration algorithm used in a titration study by Zinman et al. (2012). Dose adjustments are based on average FG of three days above target, or the lowest below target.

FG [mmol/L]	Dose adjustment
< 3.1	-4U
3.1 − 3.9	-2U
4.0 − 5.0	In target: no change
5.1 − 7.0	+2U
7.1 − 8.0	+4U
8.1 − 9.0	+6U
> 9.0	+8U

since the standard deviation in untreated T2D discussed in Section 2 is 14%. Fig 3 illustrates a comparison of FG levels and the clinical trial results. Considering the two solid lines, the clinical trial results and simulation results assuming 100% adherence, both fall within one standard deviation of the other. Furthermore, the dynamics of average FG of the cohort are similar. The results indicate that the simulation results can be used to represent changes in FG over a titration period in a clinical trial with similar starting values, patient characteristics and dose guidance.

4.2 Effect of adherence on variability and safety

To evaluate the effect of adherence on variations in FG and safety of dose guidance, we simulate a similar titration period as before but with different levels of adherence. From Fig. 2, adherence is reported to be between 60% and 90%. We choose to simulate three adherence levels, 50%, 70% and 100%, to represent three levels of adherence. Fig. 3 illustrates the FG values in the three adherence scenarios compared with the clinical data. To evaluate safety of dose guidance in the different scenarios, we measure:

- Number of FG measurements under 4 mmol/L ($FG < 4$) and 2.7 mmol/L ($FG < 2.7$).
- Glycemic coefficient of variation (FG CV).
- Number of times where recommended dose, U_r, is greater than a dose that would have brought FG under 4 mmol/L, ($U_r > U_4$), and 2.7 mmol/L, ($U_r > U_{2.7}$).
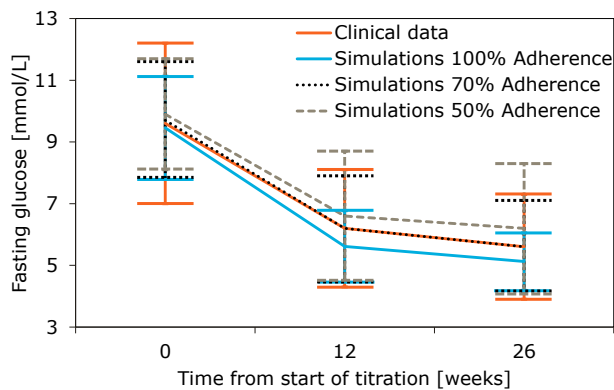

Fig. 3. Results from a clinical trial (Zinman et al., 2012) and simulations of 270 T2D patients. The results represent the same drug, the same titration algorithm, and similar inclusion criteria.

Table 3. Results from a simulated titration period of 26 weeks for adherence levels 50%, 70% and 100% (mean (standard deviation)).

Measure		Adherence 50%	70%	100%
$FG < 4$	[%]	7.7 (7.7)	6.8 (7.1)	4.9 (4.3)
$FG < 2.7$	[%]	0.4 (0.9)	0.1 (0.4)	0.0
FG CV	[%]	30.1 (5.6)	28.1 (3.7)	21.6 (2.1)
$U_r > U_4$	[%]	24.4 (27.5)	5.3 (13.8)	0.0
$U_r > U_{2.7}$	[%]	0.2 (1.1)	0.0	0.0

The results are presented in Table 3 as the percentage of days out of 26 weeks where the events listed above occur. The results indicate a difference in FG variance of the 270 patients in the three adherence scenarios. Coefficient of variation is 21.6%(2.1%) where no doses were omitted, 28.1%(3.7%) for 70% adherence and 30.1(5.6) for 50% adherence. Similarly, the results indicate that the number of times where a recommended dose U_r was larger than a dose that would lower FG below target, U_4. This never occurred in the perfect adherence case, but 5.3%(13.8%) and 24.4%(27.5%) of recommended doses for 70% and 50% adherence, respectively. However, there does not seem to be a difference in number of hypoglycemic events. A possible explanation could be when a too large dose is recommended but not injected, it will not cause hypoglycemia.

In the simulations of different adherence levels, we find that FG has a coefficient of variation between 20% and 30% on average. This is lower than the 35% mentioned in Section 2. It must be pointed out that this simulation only assumes 14% biological variance in FG and does not take PK/PD variance into account.

5. CONCLUSIONS

This paper presents a review of sources of variance in long-acting insulin treatment for T2D patients and suggests a categorization. Biological variance caused by PK/PD of insulin varies greatly between types of basal insulin. Accuracy of devices is a minor factor compared with other variance sources including biological variance and adherence to treatment. It should be noted that the group of T2D patients more heterogeneous than T1D. Categorizing sources of variability in T2D is not necessarily as simple as for T1D, as it may be different depending on the severity of the disease.

We suggest a model of glucose-insulin dynamics to generate a cohort of T2D patients initiating long-acting insulin treatment. The results indicate that the model is sufficient to simulate FG levels of T2D patients in-silico during a long-acting insulin titration period. Results from comparing dose suggestions and FG levels in different adherence scenarios indicate that dose guidance algorithms should take adherence into account to ensure safe dose guidance. We should furthermore mention that adherence is evidently crucial to reaching recommended goals in insulin treatment. We have shown that adherence is essential to safe treatment when using dose guidance algorithms.

The motivation for creating this model was to simulate FG values in T2D during a titration period. For the purpose of bolus calculations and more detailed meal

simulations, the model parameters related to carbohydrate uptake should be refined. Also the choice of endogenous insulin production model should be improved to allow daily fluctuations.

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